

Title	Vitamin D and muscle strength throughout the life course: a review of epidemiological and intervention studies.
Authors	McCarthy, Elaine K.;Kiely, Mairead E.
Publication date	2014-10-03
Original Citation	McCarthy, E. K. and Kiely, M. (2015) 'Vitamin D and muscle strength throughout the life course: a review of epidemiological and intervention studies', Journal of Human Nutrition and Dietetics, 28(6), pp. 636-645. doi: 10.1111/jhn.12268
Type of publication	Article (peer-reviewed)
Link to publisher's version	https://onlinelibrary.wiley.com/doi/full/10.1111/jhn.12268 - 10.1111/jhn.12268
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Download date	2023-05-05 13:07:04
Item downloaded from	http://hdl.handle.net/10468/7522



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1 **Article Type**

2 State of the art review

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4 **Title**

5 Vitamin D and muscle strength throughout the life course: a review of epidemiological and
6 intervention studies

7

8 **Running Head**

9 Vitamin D and muscle strength

10

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22

23 **Role of Authors**

24 Both authors contributed equally to this review.

25

26 **Key Words**

27 Muscle function, muscle strength, vitamin D, vitamin D receptor, vitamin D deficiency.

28

29 The authors have no conflicts of interest and no sources of funding to declare for this manuscript.

30

31 Abstract

32

33 The putative role for vitamin D in muscle function and strength throughout the life course is of interest
34 as muscle strength is required for engagement in physical activity at all ages. As vitamin D deficiency
35 is widely reported in the population, especially in countries at high latitude, the potential importance
36 of vitamin D in muscle function throughout life, and potential impacts on growth and development,
37 participation in physical activity and effects on skeletal and cardio-metabolic health, is an important
38 topic for discussion. This review provides an overview of muscle function and summarises the role
39 of the vitamin D receptor and proposed molecular mechanisms of action of vitamin D in muscle cells.
40 In addition, the review provides a comprehensive assessment of the clinical evidence surrounding the
41 association between vitamin D and muscle strength. Among adults, particularly older adults, cross-
42 sectional and cohort studies reported a positive association between vitamin D status and muscle
43 strength. These associations have been largely confirmed by intervention studies. Limited research
44 has been carried out in adolescents and children; two cross-sectional studies in adolescents have
45 suggested an association between serum 25-hydroxyvitamin D concentrations and muscle strength.
46 However, the two intervention studies in adolescents have yielded conflicting results. Other than a
47 single observational study, data in young children are very limited and further investigation in under
48 12's is warranted.

49 **Introduction**

50

51 The adverse outcomes of vitamin D deficiency, such as nutritional rickets in children and adolescents
52 and osteomalacia and osteoporosis in adults, are well-documented (Institute of Medicine, 2011).
53 However, vitamin D deficiency has also been linked with muscle weakness in both children and
54 adults, suggesting additional indirect benefits of vitamin D on skeletal health beyond its well-
55 established role in calcium homeostasis (van der Heyden *et al.*, 2004). Muscle weakness, particularly
56 affecting proximal muscles with symptoms such as delayed onset of walking in infants and difficulty
57 climbing stairs in adolescents, is a clinical manifestation of vitamin D deficiency, which may coexist
58 with skeletal features such as rickets and hypocalcaemia (Shaw and Mughal, 2013). The aim of this
59 review is to examine the association between vitamin D and muscle strength throughout the life
60 course, with a particular emphasis on the available clinical evidence.

61

62 Searches for this review were conducted in PubMed and Web of Science and terms (Mesh terms
63 where applicable) included "Vitamin D" OR "Ergocalciferols" OR "Vitamin D Deficiency" OR
64 "Cholecalciferol" OR "Vitamin D Receptor" AND "Muscles" OR "Muscle Strength" OR "Muscle
65 Cells" OR "Muscle Development" OR "Muscle Weakness" OR "Genomic Pathway" OR "Non-
66 genomic Pathway". A manual search of bibliographies of relevant primary journal articles was also
67 conducted, with searches restricted to articles in English and citations up to June 2014.

68

69 A brief summary of some studies in older adults has been provided, including results from meta-
70 analyses, as research into this area is well developed. For younger adults, adolescents and children,
71 this review provides a complete and exhaustive review of all relevant studies on this topic to date.

72

73 **Background**

74

75 *Vitamin D*

76 Decreased serum 25-hydroxyvitamin D (25(OH)D) concentrations and vitamin D deficiency are
77 widespread across the world with the highest rates of severe deficiency found in South Asia and the
78 Middle East (van Schoor and Lips, 2011). In Europe, there is much variability in serum 25(OH)D
79 concentrations; a recent systematic review from Hilger *et al.* (2014) reported that the highest
80 concentrations in Europe were in Sweden. Serum 25(OH)D concentration is the most commonly

81 used, reliable and robust biomarker of vitamin D status (Seamans and Cashman, 2009). Currently,
82 there is no consensus among experts as to the definitive threshold concentration for vitamin D
83 deficiency. The US Institute of Medicine proposed that a serum 25(OH)D concentration of 50 nmol/L
84 would cover the requirements 97.5% of the population for the maintenance of skeletal health and
85 suggested a vitamin D deficiency cut-off value of 30 nmol/L (Institute of Medicine, 2011).

86

87 Serum 25(OH)D concentrations are dependent on various factors, mainly cutaneous production in the
88 presence of UVB and dietary intake. There are a limited amount of foods containing naturally
89 occurring vitamin D but some natural sources include oily fish, meat, dairy, egg yolk and mushrooms
90 (Gonzalez-Rodriguez *et al.*, 2013) and depending on legislation, some foods are fortified with vitamin
91 D, including milk, yoghurt, spreads, cheese, juices, breads and breakfast cereals (Kiely and Black,
92 2012). However it appears that dietary sources alone cannot supply an individual with all their
93 vitamin D needs (Heaney *et al.*, 2003), with variations in vitamin D intakes from dietary sources
94 occurring due to country specific fortification practices, sex, age, and supplement use practices
95 (Cashman and Kiely, 2014). Therefore the cutaneous production of vitamin D is a major determinant
96 of serum 25(OH)D concentrations and vitamin D status. However there are several environmental
97 factors that impede year-round synthesis, such as latitude and prevailing weather conditions.
98 Cutaneous production can also be affected by skin pigmentation, age, attire, sunscreen, working
99 environment, physical activity and sun exposure behaviour (Kiely and Black, 2012).

100

101 *Muscle Contraction and Muscle Function*

102 To understand how vitamin D can impact on muscle function and strength, the mechanisms of action
103 of muscle cells must be considered. Muscle cells are composed of subunits called myofibrils and
104 each myofibril is composed of smaller structures called myofilaments. There are two main types of
105 myofilament in muscle cells; thick filaments, composed of the protein myosin, and thin filaments,
106 composed of the protein actin (Fox, 2009). Filaments are arranged within subunits known as
107 sarcomeres; the fundamental functional units of muscle. The release of an action potential from the
108 brain spreads into muscle fibres and causes a release of calcium ions (Ca^{2+}) from the sarcoplasmic
109 reticulum into the nearby actin-myosin complex. Ca^{2+} binds to the protein troponin which results in
110 excitation-contraction coupling of the muscle cell (Dulhunty, 2006). Within the myosin filament, an
111 adenosine triphosphate (ATP) molecule is split by myosin ATPase enzymes and the release of a
112 phosphate results in a conformational change in the myosin filament, causing a cross-bridge with
113 actin to produce a power stroke. This power stroke results in the sliding of thick and thin filaments

114 over each other, also known as muscle contraction. The joining of a second ATP molecule to the
115 myosin head results in the uncoupling of myosin and actin and thus muscle relaxation (Fox, 2009).

116

117 *Is the vitamin D receptor present in muscle?*

118 The active metabolite of vitamin D, 1,25 dihydroxyvitamin D (1,25(OH)₂D) elicits its effects on
119 calcium homeostasis through a vitamin D receptor (VDR); 1,25(OH)₂D binds to the VDR on the cell
120 cytosol resulting in a change in gene expression of that cell. VDR have now been located in more
121 than 30 tissues in the body, not just tissues involved in calcium homeostasis (Zittermann, 2003).
122 However, the presence of VDR in muscle tissue is still a debated topic. One of the earliest studies by
123 Simpson *et al.* (1985) in cultured rat muscle cells suggests that 1,25(OH)₂D can act directly on muscle
124 through a VDR that is similar to the receptors found in bone and the intestines. Boland *et al.* (1985)
125 demonstrated the presence of VDR in monolayers of chick myoblasts and Costa *et al.* (1986)
126 demonstrated similar results in cloned human skeletal muscle cells. In a study using VDR gene-
127 deleted mice, Endo *et al.* (2003) demonstrated that the absence of VDR in these mice caused muscle
128 abnormalities, supporting the hypothesis of physiological roles of direct VDR actions on skeletal
129 muscle cells. Studies by Bischoff *et al.* (2001), Bischoff-Ferrari *et al.* (2004a) and more recently
130 Ceglia *et al.* (2010) have demonstrated the presence of VDR in skeletal muscle cells using human
131 muscle cell samples. However, Wang and DeLuca (2011) have contradicted earlier findings
132 demonstrating that VDR were not detected in skeletal, smooth or cardiac muscle, using human, mouse
133 and rat muscle tissues. They suggest that the function of vitamin D on muscle does not involve this
134 receptor and may be of an indirect nature. Despite some debate, it is widely thought that VDR are
135 located in muscle cells and that the VDR acts as a mediator for 1,25(OH)₂D to elicit its effects on
136 muscle, however this is a point that requires further clarification.

137

138 Three adjacent restriction fragment length polymorphisms for *BsmI*, *ApaI*, and *TaqI* at the 3' end of
139 the VDR gene have been extensively studied (Uitterlinden *et al.*, 2004). Most studies that have looked
140 at musculoskeletal health have focused on the *BsmI* polymorphism. Geusens *et al.* (1997) assessed
141 quadriceps strength in 501 elderly women and those with the *bb* allele had maximal isometric strength
142 23% higher than those with the *BB* allele and 12% higher than those with the *Bb* allele. However, no
143 such association was found by Windelinckx *et al.* (2007) in 493 adults in Belgium. Other studies
144 have identified the risk of falling as a measure of muscle strength. Results from the iLSIRENTE study
145 of 259 elderly men and women, found an association between the *bb* allele of the *BsmI* polymorphism
146 and a reduced risk of falling compared to those with the *BB* allele (Onder *et al.*, 2008). Similar results

147 were subsequently reported by Barr *et al.* (2010) in 2374 elderly women. These studies suggest that
148 an association between certain VDR gene polymorphisms and muscle strength may exist. However,
149 further research is required to confirm these findings and to provide further understanding of the role
150 of VDR genetic polymorphisms in muscle function and strength.

151

152 *Molecular mechanisms of action of vitamin D in muscle tissue*

153 The mechanisms through which vitamin D can influence muscle function and strength are still unclear
154 but it is thought that there are two main pathways through which 1,25(OH)₂D functions: the genomic
155 pathway and the non-genomic pathway. Once 1,25(OH)₂D has been transported to the nucleus of a
156 muscle cell, it can elicit a slow, genomic transcriptional effect through binding to VDR, causing
157 destabilization of a VDR complex in the VDR response element in the promoter region of a gene. At
158 the same time as this destabilization and in the presence of the retinoic receptor (RXR), the formation
159 of the VDR–RXR heterodimer occurs (Cheskis and Freedman, 1994). This heterodimer can then
160 promote an interaction between the VDR's zinc finger region and DNA, resulting in mRNA
161 transcription and ultimately *de novo* protein synthesis (Freedman, 1999). The synthesis of proteins
162 including the calcium binding proteins calmodulin and calbindin D_{9K} can be altered by the genomic
163 pathway of 1,25(OH)₂D. These proteins are usually involved in muscle cell calcium uptake, muscle
164 cell proliferation and differentiation and phospholipid metabolism (Ceglia, 2008).

165

166 The rapid, non-genomic effects of 1,25(OH)₂D are also thought to be mediated by VDR, as the
167 presence of 1,25(OH)₂D in muscle cells can induce the translocation of nuclear VDR into the plasma
168 membrane of cells (Capiati *et al.*, 2002). Non-genomic effects of 1,25(OH)₂D involve the activation
169 of a number of cell signalling pathways including protein kinase C, calmodulin-dependent kinase and
170 many others. Calcium homeostasis is affected by the non-genomic pathway, as the actions of
171 1,25(OH)₂D can result in a rapid influx of calcium from the sarcoplasmic reticulum which can play
172 a role in regulating muscle cell contractions. Non-genomic effects of 1,25(OH)₂D also include the
173 stimulation of proliferation and differentiation of muscle cells, protection of skeletal muscle cells
174 from insulin resistance and induction of the release of arachidonic acid which can alter cell membrane
175 fluidity and permeability (Dirks-Naylor and Lennon-Edwards, 2011). Although many of the non-
176 genomic effects of 1,25(OH)₂D have been well described, there is still uncertainty as to how important
177 these pathways are in the body and as to how exactly vitamin D acts in muscle cells.

178

179 **Effects of vitamin D deficiency on muscle**

180

181 Vitamin D deficiency ($25(\text{OH})\text{D} < 30 \text{ nmol/L}$) can have adverse effects in both skeletal and cardiac
182 muscle cells. Dilated cardiomyopathy (DCM), secondary to severe vitamin D deficiency and
183 hypocalcaemia, is a potentially fatal condition affecting cardiac muscle cells. In a review of the
184 prevalence of DCM in paediatric cardiology units in Southeast England, 16 cases of rickets-associated
185 heart failure were seen over a six-year time frame. Of these 16 cases, six of the infants had a cardiac
186 arrest, two were referred for cardiac transplantation and a further three died. Predisposing factors
187 leading to the severe vitamin D deficiency that resulted in DCM were dark skin and exclusive
188 prolonged breastfeeding, with the majority of cases presenting during British wintertime. None of
189 the infants or their mothers took vitamin D or calcium supplements during the pre- or postnatal period,
190 however maternal serum $25(\text{OH})\text{D}$ concentrations were not reported in many cases (Maiya *et al.*,
191 2008). Subsequent case studies from Brown *et al.* (2009), Al Azkawi and Al Mutair (2012) and
192 Sanyal and Raychaudhuri (2013) reported of infants presenting with DCM; further analysis revealed
193 that they had rickets and severe hypocalcaemia due to vitamin D deficiency. Treatment with calcium
194 and vitamin D resulted in a rapid recovery of cardiac function in most cases.

195

196 The focus of this review is vitamin D and skeletal muscle. Muscle weakness and pain are
197 characteristics of rickets and osteomalacia. A detailed review of symptomatic vitamin D deficiency
198 and rickets as well as muscle-related symptoms in affected children and adolescents, including
199 reluctance to bear weight, pain and weakness has been provided by Shaw and Mughal (2013).
200 Likewise in adults, muscle pain and weakness are also symptoms of vitamin D deficiency, which can
201 result in more specific proximal muscle deficits, including an inability to climb stairs, lift objects or
202 rise from a seated/squat position (Girgis *et al.*, 2013). Findings of muscle weakness and pain in the
203 bone diseases rickets and osteomalacia are unsurprising; muscle and bone growth and development
204 are closely connected. Muscle is the main mechanical stimulus for bone tissue growth and
205 development as they cause the largest load and strain on bone and this strain is essential for control
206 of the biological mechanisms determining whole-bone strength (Frost and Schonau, 2000). Much
207 research is still required as little is known about the cellular interactions between muscle and bone,
208 with a need to investigate muscle and bone interactions together as opposed to looking at each tissue
209 separately (Bonewald *et al.*, 2013).

210

211 Given the close interaction between muscle and skeletal development, there is a dearth of information
212 on interactions between vitamin D status and bone and muscle development in children. Among
213 older adults, the clinical observational and experimental literature is relatively well developed albeit
214 controversial.

215

216 *Older Adults*

217 Many of the studies performed in older adults have used lower extremity function tests to assess
218 muscle strength, including walking speed/gait tests, chair stands and tandem tests. Handgrip strength
219 and thigh muscle strength as measured by a dynamometer have also been used. An adverse health
220 consequence of poor muscle strength or muscle weakness in older adults is the increased risk of
221 falling. Lean mass as measured using techniques including dual energy x-ray absorptiometry (DXA)
222 has also been studied, with some studies suggesting a positive association between it and serum
223 25(OH)D concentrations (Lee, 2013). However, the focus of this review is on vitamin D and its
224 effects on measures of muscle strength and function, not on the size of muscles. In a large sample of
225 4100 men and women aged ≥ 60 years, Bischoff-Ferrari *et al.* (2004b) showed better lower extremity
226 functioning in adults with serum 25(OH)D concentrations ≥ 40 nmol/L compared with those with
227 25(OH)D concentrations < 40 nmol/L. Similarly, Wicherts *et al.* (2007) found in 1234 men and
228 women (mean age 75 years) that 25(OH)D concentrations < 50 nmol/L were associated with lower
229 scores for lower extremity functioning and a greater decline in physical performance over the three-
230 year study. While 25(OH)D concentrations of 80 nmol/L or above have been suggested by some
231 investigators (Dawson-Hughes, 2008, Dam *et al.*, 2009) as optimal to promote muscle function in
232 older adults, findings from observational studies have suggested that a serum 25(OH)D concentration
233 of less than 50 nmol/L appears to detrimentally affect muscle function and strength.

234

235 Findings from intervention studies in older adults are conflicting despite a multitude of literature in
236 this age group. Flicker *et al.* (2005) randomised 625 adults (mean age 83 years) to receive either
237 placebo or vitamin D₂ (10,000IU [250 μ g] once weekly initially and then 1,000IU daily) plus 600mg
238 calcium for two years. Those compliant with the vitamin D treatment had a reduced incidence of
239 falls compared to the placebo group, regardless of baseline 25(OH)D concentrations. Pfeifer *et al.*
240 (2009) randomised 242 adults (mean age 77 years) to receive either 1000mg calcium or 1000mg
241 calcium plus 800IU vitamin D₃ daily for 12 months. Vitamin D plus calcium supplementation
242 significantly reduced the number of falls in participants compared to the calcium only treatment group
243 and significant improvements in measures of muscle strength (quadriceps strength, lower extremity

functioning) were also reported in the vitamin D treatment group. Zhu *et al.* (2010) randomised 302 women (aged 70-90 years) to receive either 1000IU vitamin D₂ plus 1000mg calcium or just 1000mg calcium daily for one year. Increased muscle function (maximal contraction of various muscle types) was observed in those in the lowest tertile for baseline muscle strength in this group of women with baseline 25(OH)D concentrations <60 nmol/L.

249

Conflicting findings were reported in a study of 243 older adults by Latham *et al.* (2003); participants were randomised to receive a single oral dose of 300,000IU vitamin D₃ or placebo and muscle strength (lower extremity functioning) was assessed six months after supplementation. There were no improvements in muscle strength measures after supplementation, even in those with 25(OH)D concentrations <30 nmol/L at baseline. Janssen *et al.* (2010) randomised 70 females aged >65 years with baseline 25(OH)D concentrations <50 nmol/L to receive either 400IU vitamin D₃ plus 500mg calcium or placebo plus 500mg calcium daily for six months. Despite observing significant positive associations between 25(OH)D concentrations and muscle strength at baseline, there were no improvements in muscle strength in either treatment group after six months. Glendenning *et al.* (2012) randomised 686 women (mean age 77 years) to receive 150,000IU vitamin D₃ or placebo every three months for nine months. Vitamin D supplementation was ineffective in reducing the number of falls in these women (mean baseline 25(OH)D of 65.8 nmol/L). The high-dose intermittent supplementation regimen used in this study and by Latham *et al.* (2003) may explain the lack of effect on muscle strength as it has been suggested that high-dose supplementation may alter gene regulation and negate any beneficial effects of vitamin D on muscle metabolism. Similar findings on dose regimen have been reported in a meta-analysis from Muir and Montero-Odasso (2011) where the authors suggest that supplemental daily doses of 800-1000IU of vitamin D demonstrate beneficial effects on muscle strength consistently, with inconsistent findings for high-dose treatments.

268

The heterogeneity of studies in older adults carried out to date as highlighted here, have made it difficult to draw conclusions from their results, as differences exist in the study populations assessed, treatment durations, muscle strength measures, doses and types of vitamin D used and the use of additional supplementation including calcium. These issues were highlighted in the recent report from the US Institute of Medicine and it declared that there was inconsistent evidence that vitamin D supplementation reduced the risk of falling in older adults (Institute of Medicine, 2011). This finding is in contrast to many earlier studies including a meta-analysis by Bischoff-Ferrari *et al.* (2009) that observed a 19% reduction in falls with daily vitamin D supplementation of 700-1000IU. However,

277 the Institute of Medicine did claim that this particular meta-analysis was flawed in its choice of studies
278 and its method chosen to explain the heterogeneity of studies. Despite these conflicting arguments,
279 further meta-analyses have suggested that daily vitamin D plus calcium supplementation can improve
280 muscle strength and reduce the risk of falls, especially in individuals with 25(OH)D concentrations
281 <25 nmol/L (Stockton *et al.*, 2011, Murad *et al.*, 2011). Further large randomised controlled trials
282 with standardised muscle strength measures are required to clarify the issues surrounding the role of
283 vitamin D in muscle strength in older adults.

284

285 *Young Adults*

286 Until recently, much less research had been conducted in younger adults. A recent observational
287 study by Grimaldi *et al.* (2013) in 419 adults (mean age 44 years, 8% had 25(OH)D <50 nmol/L),
288 observed a positive association between 25(OH)D concentrations and muscle strength, most notably
289 for arm muscles. A smaller study of 137 women aged 19 to 29 years (mean 25(OH)D of 54 nmol/L)
290 also found a significant positive association between 25(OH)D concentrations and muscle strength
291 (handgrip strength) (von Hurst *et al.*, 2013). Similar findings were reported in a very small study (*n*
292 22) of Muslim women living in Canada with mean 25(OH)D concentrations of 36 nmol/L (Ojah and
293 Welch, 2012). Contrastingly, no association between 25(OH)D concentrations and muscle strength
294 was found in a study of 1219 men (mean age 48 years) by Ceglia *et al.* (2011). Reasons for these
295 conflicting findings may be because the study population assessed by Ceglia *et al.* (2011) only
296 consisted of males and the age range of participants was very broad (30-70 years), which is in contrast
297 to the population groups assessed in other studies.

298

299 Diamond *et al.* (2013) randomised 30 adults (25(OH)D at baseline <50 nmol/L) to receive either 2000
300 or 5000IU vitamin D₃ daily for three months; improvements in handgrip strength were observed in
301 both treatment groups. In India, 40 adults (mean age 31 years, 25(OH)D at baseline <50 nmol/L)
302 were randomised to receive either placebo or 60,000IU vitamin D₃ per week for the first eight weeks,
303 followed by 60,000IU vitamin D₃ per month for four months plus 1000mg calcium daily for six
304 months. Muscle strength (handgrip/thigh muscle strength, lower extremity functioning) increased
305 significantly higher in the supplemented group compared to the placebo group (Gupta *et al.*, 2010).
306 However in a similar study performed subsequently by the same research group in 173 females (mean
307 age 22 years), no significant change in muscle strength was observed following vitamin D and
308 calcium supplementation (Goswami *et al.*, 2012). A reason for the lack of an effect may be that
309 vitamin D and calcium supplementation does not improve handgrip strength in young adult females,

310 as when results from their earlier study were reanalysed by sex, it revealed that improvements in
311 handgrip strength occurred only in males. In a study of non-Western immigrant adults in Norway
312 (mean 25(OH)D at baseline of 27 nmol/L), supplementation of 400 or 1000IU vitamin D₃ daily for
313 16 weeks did not improve muscle strength (handgrip strength, jump height) (Knutsen *et al.*, 2014).
314 Similar findings were also reported by Wicherts *et al.* (2011) in a study of non-Western immigrant
315 adults in The Netherlands. Contrastingly, a study in male athletes by Close *et al.* (2013) reported
316 significant increases in muscle strength (jump height, endurance tests) after an eight-week
317 intervention of 5000IU vitamin D₃ daily, in the treatment group compared to the placebo group.

318

319 Similarly to the findings in older adults, there are conflicting findings regarding younger adults, albeit
320 less research has been conducted in this age group. There is a need for further long-term intervention
321 studies in this age group in both males and females to determine the role of vitamin D in muscle
322 strength during early adult life.

323

324 *Adolescents and Children*

325 Currently, there are limited data available on the role of vitamin D in muscle strength in adolescents
326 and children and most of the data that are available are in older children or adolescents (Table 1). In
327 an observational study of 99 post-menarchal females (aged 12-14 years), a positive association
328 between 25(OH)D concentrations and muscle strength (jumping mechanography) was observed.
329 Those with lower 25(OH)D concentrations generated less power during jumping and had lower jump
330 height and velocity (Ward *et al.*, 2009). In another study of 301 females aged 15 years in China,
331 participants with 25(OH)D concentrations >50 nmol/L had significantly greater handgrip strength
332 compared to those with lower 25(OH)D concentrations, independent of body size, dietary intakes of
333 vitamin D and calcium and levels of physical activity (Foo *et al.*, 2009).

334

335 El-Hajj Fuleihan *et al.* (2006) randomised 179 females aged 10-17 years (mean 25(OH)D at baseline
336 of 35 nmol/L) to receive either 1400IU vitamin D₃ per week (low dose), 14,000IU vitamin D₃ per
337 week (high dose) or a placebo weekly for one year. There were significant increases in lean mass
338 (measured by DXA) in both the low and high dose treatment groups compared to the placebo group,
339 despite no significant change in handgrip strength between the treatment groups. The changes in lean
340 mass observed in this study perhaps suggest a direct effect of vitamin D on muscle size, however the
341 lack of effect on handgrip strength may indicate that this measure is not sensitive enough to detect

342 slight changes in muscle strength in children and adolescents. Seventy-three 12-14 year old females
343 (25(OH)D at baseline <37.5 nmol/L) were randomised to receive either 150,000IU vitamin D₂ or a
344 placebo every three months for 12 months. Mixed findings for muscle strength (jumping
345 mechanography, handgrip strength) were observed, with improved jumping efficacy observed in the
346 treatment group, but not jump power or force or handgrip strength (Ward *et al.*, 2010). These mixed
347 findings for muscle strength may be explained by the suggestion by Glendenning *et al.* (2012) that
348 intermittent high-dose supplementation may alter gene regulation and negate any beneficial effects
349 of vitamin D on muscle metabolism. The very limited evidence from intervention studies in
350 adolescents and older children have produced conflicting findings. Further research is required in
351 this age group and in younger children to determine if vitamin D can impact on muscle strength in
352 early childhood. The focus of research should be to perform large randomised controlled trials in
353 both males and females, providing daily/weekly vitamin D supplementation at a dose that will not
354 have adverse health effects.

355

356 Recently the relationship between intrauterine 25(OH)D exposure and muscle strength in children
357 has been explored. A study from the Southampton Women's Survey reported a significant positive
358 association between maternal 25(OH)D concentrations at 34-weeks' gestation and height adjusted-
359 handgrip strength in their four-year old children (Harvey *et al.*, 2014). Findings from this study
360 suggest that childhood muscle strength may also be influenced by maternal vitamin D status during
361 pregnancy, suggesting the possibility of an early programming effect.

362

363 **Conclusion**

364

365 Vitamin D deficiency is now widely recognised as a public health problem of growing concern,
366 particularly for populations at increased risk due to high latitude, prolonged winter season, or other
367 reasons for restricted UVB exposure and low vitamin D intake. Apart from the acknowledged links
368 between muscle myopathy and nutritional rickets and osteomalacia, there is evidence for a biological
369 role for vitamin D in muscle function. Much of the clinical studies have focused on older adults,
370 where an association between serum 25(OH)D concentrations below 50 nmol/L and reduced muscle
371 strength appears to be inconsistent. Data among younger adults and adolescents are few and
372 conflicted. Partly due to the challenges involved in measuring muscle strength in young children,
373 where methods such as jumping mechanography and lower extremity function tests can be difficult
374 to perform and replicate, the data in children are few and far between. New approaches to assess

375 muscle strength in young children are required. Due to these difficulties and some inconsistent
376 findings, clinical guidelines on vitamin D for muscle strength and function are limited. Current
377 population guidelines regarding vitamin D are to avoid deficiency with the aim to have vitamin D
378 intakes at the level of the Recommended Dietary Allowance (RDA) set by the national governing
379 authority. Despite recommendations, suboptimal serum 25(OH)D concentrations amongst
380 adolescents and children have been reported all around the world, including India (Marwaha *et al.*,
381 2005), the Middle East (El-Hajj Fuleihan *et al.*, 2006), North America and Canada (Newhook *et al.*,
382 2009, Sullivan *et al.*, 2005), Ireland (Hill *et al.*, 2008), the UK (Absoud *et al.*, 2011) and throughout
383 Europe (Gonzalez-Gross *et al.*, 2012). Therefore, the potential importance of vitamin D in muscle
384 function and strength throughout life, impacting on normal growth and development, participation in
385 physical activity and concomitant impacts on skeletal and cardio-metabolic health, is an important
386 topic for discussion. The aim of future research should be to further assess the importance of adequate
387 serum 25(OH)D concentrations throughout the life course in the development of muscle and
388 maintenance of physical performance.

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Accepted Manuscript

599 **Table 1** Vitamin D and muscle strength in children and adolescents

Study	No. of Subjects	Age	Sex	Muscle Strength Measure	Treatment Regimen	Main Outcomes
Cross-sectional						
Ward <i>et al.</i> , 2009	99	12-14y	Female	Jumping Mechanography	Not Applicable	Significant positive association between 25(OH)D concentrations and muscle power, force, velocity and jump height.
Foo <i>et al.</i> , 2009	301	15y	Female	Handgrip strength	Not Applicable	Participants with 25(OH)D concentrations >50 nmol/L had significantly greater handgrip strength compared to those with lower 25(OH)D concentrations.
Harvey <i>et al.</i> , 2014	678	4y	Male Female	Handgrip strength	Not Applicable	Significant positive association between maternal 25(OH)D concentrations at 34-weeks' gestation and handgrip strength in their four-year old children.
Intervention						
El-Hajj Fuleihan <i>et al.</i> , 2006	179	10-17y	Female	Handgrip strength	1400IU vitamin D ₃ or 14,000IU vitamin D ₃ or placebo weekly for 1 year	No significant improvements in handgrip strength in either of the vitamin D treatment groups.
Ward <i>et al.</i> , 2010	73	12-14y	Female	Jumping Mechanography, Handgrip strength	150,000IU vitamin D ₂ or placebo every 3 months for 12 months	Improved jumping efficacy in the vitamin D treatment group, but no improvements in jump power, force or handgrip strength.

600 25(OH)D, serum 25-hydroxyvitamin D; IU, international units